EPA Follow-Up Briefing to Chemical Substitutions Committee

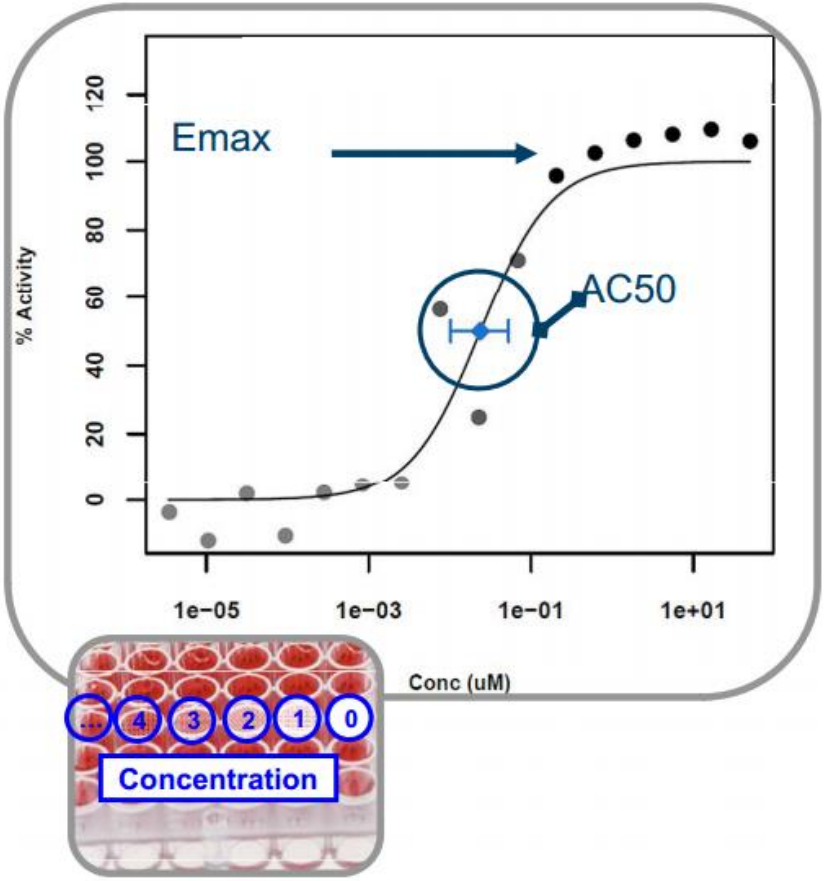
Rusty Thomas, Ph.D.
Director, National Center for Computational Toxicology
(Thomas.Russell@epa.gov)

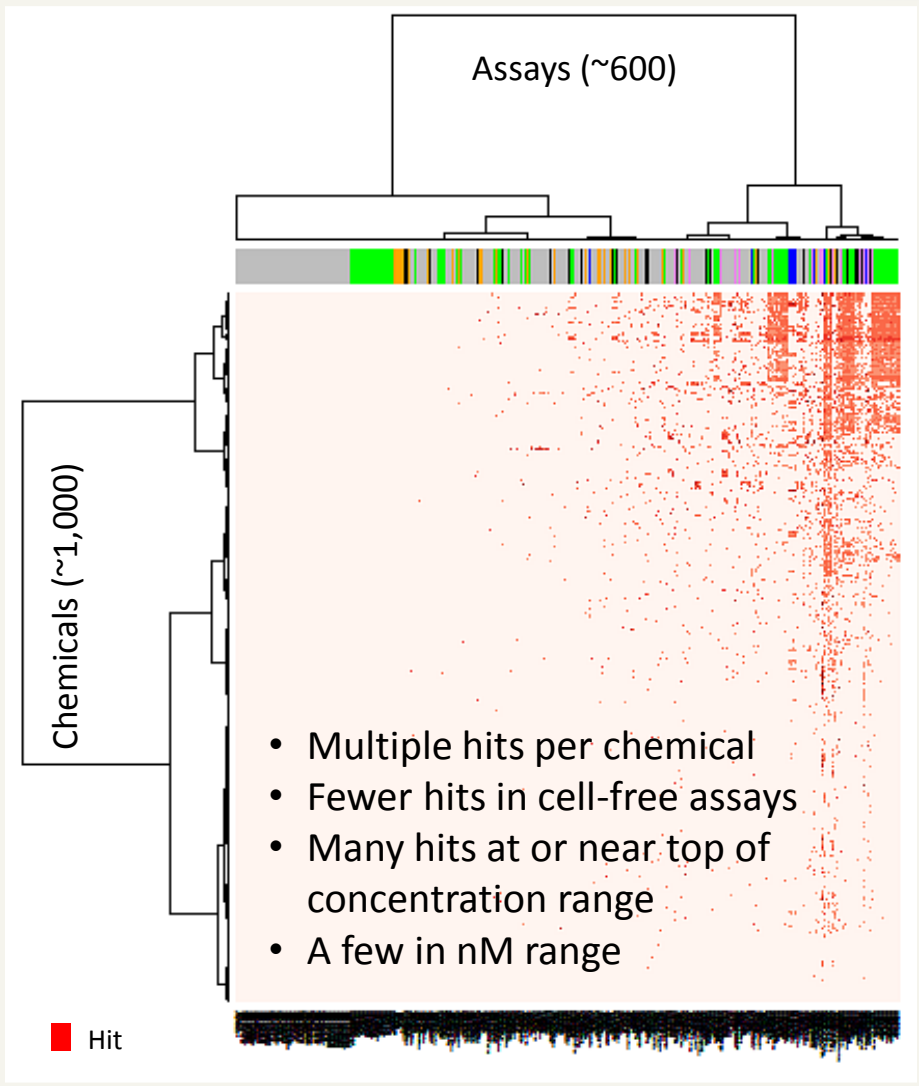
Items to Cover

- **My views on how new data streams can be used to evaluate chemical substitutions or "new chemical" design**
- **Focus on high-throughput *in vitro* assays**
- **Review of example provided by my predecessor**

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

Characteristics of the ToxCast High-Throughput Screening Data

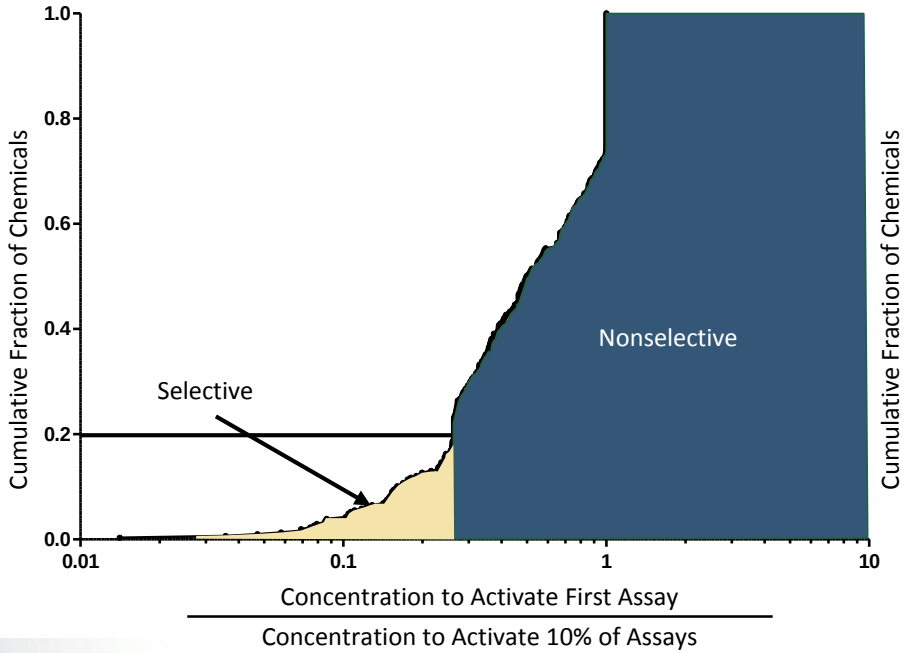


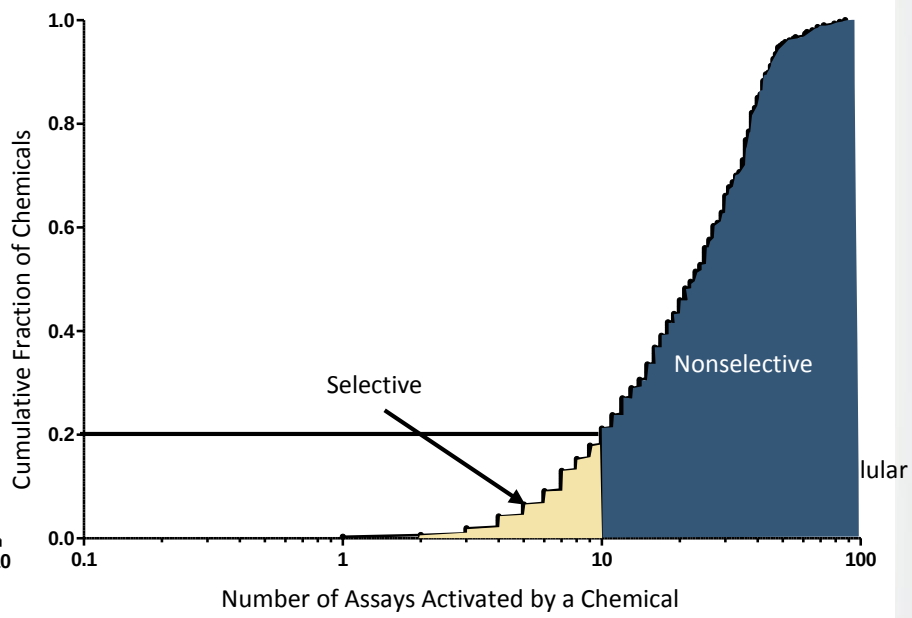


- Multiple hits per chemical
- Fewer hits in cell-free assays
- Many hits at or near top of concentration range
- A few in nM range

Many Chemicals Show Non-Selective Interactions with Biological Targets

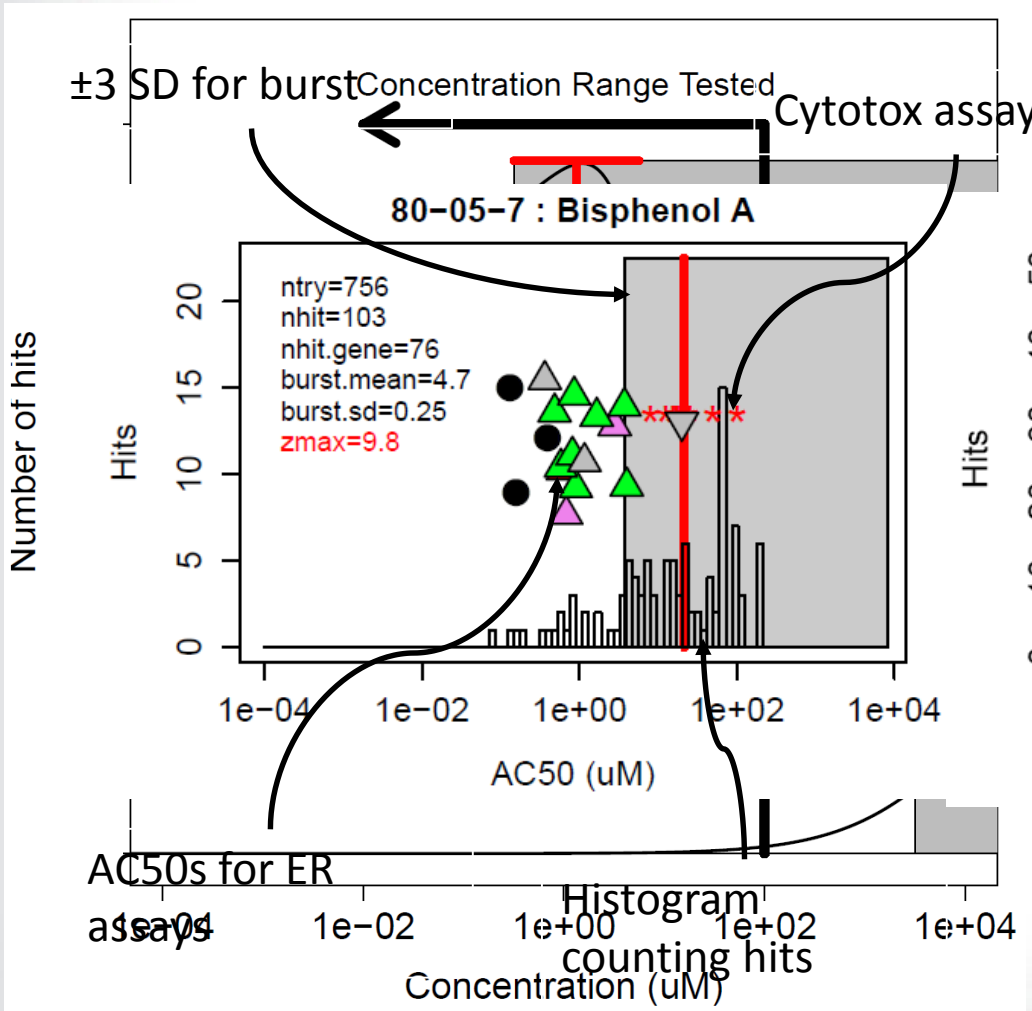
Analysis of the ToxCast Phase I Data



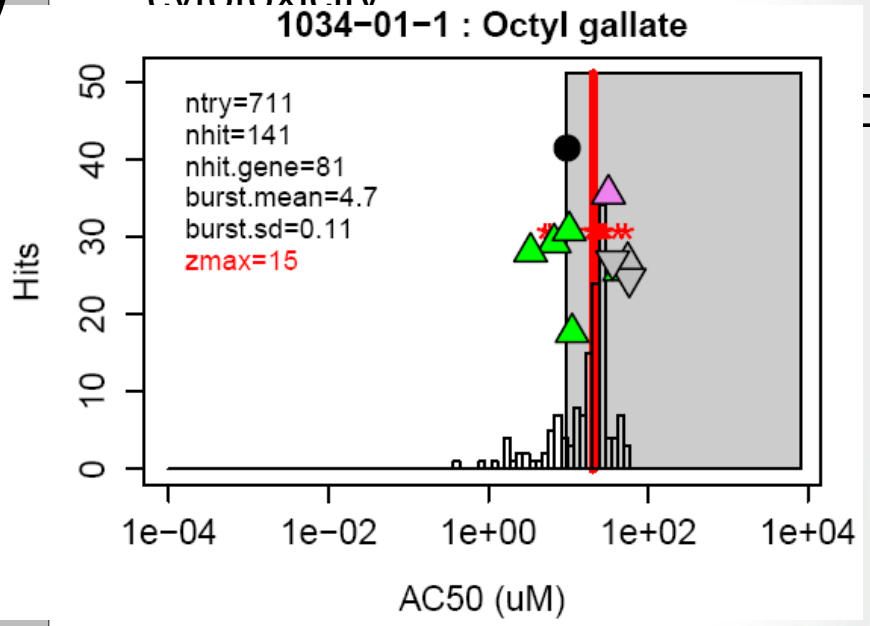


Thomas *et al., Tox Sci.,* 2013

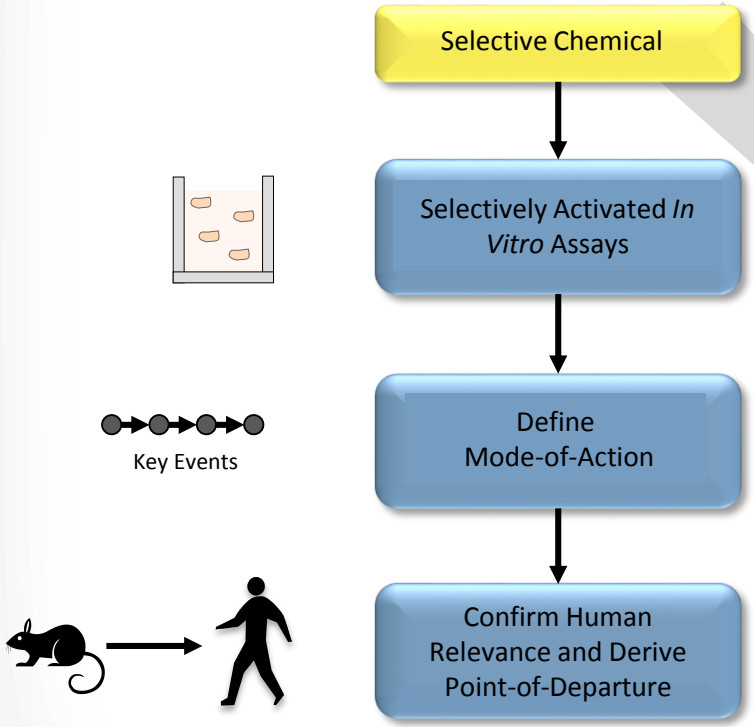
Understanding Basis of Chemical Non-Selectivity

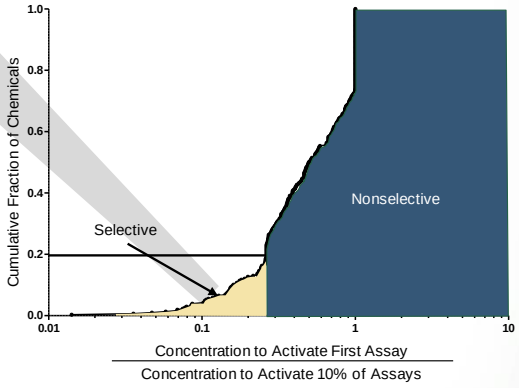


- Many chemicals showed "burst" of assay activity in the range of cytotoxicity



Chemical Selectivity as a Starting Point for Mode-of-Action / AOPs

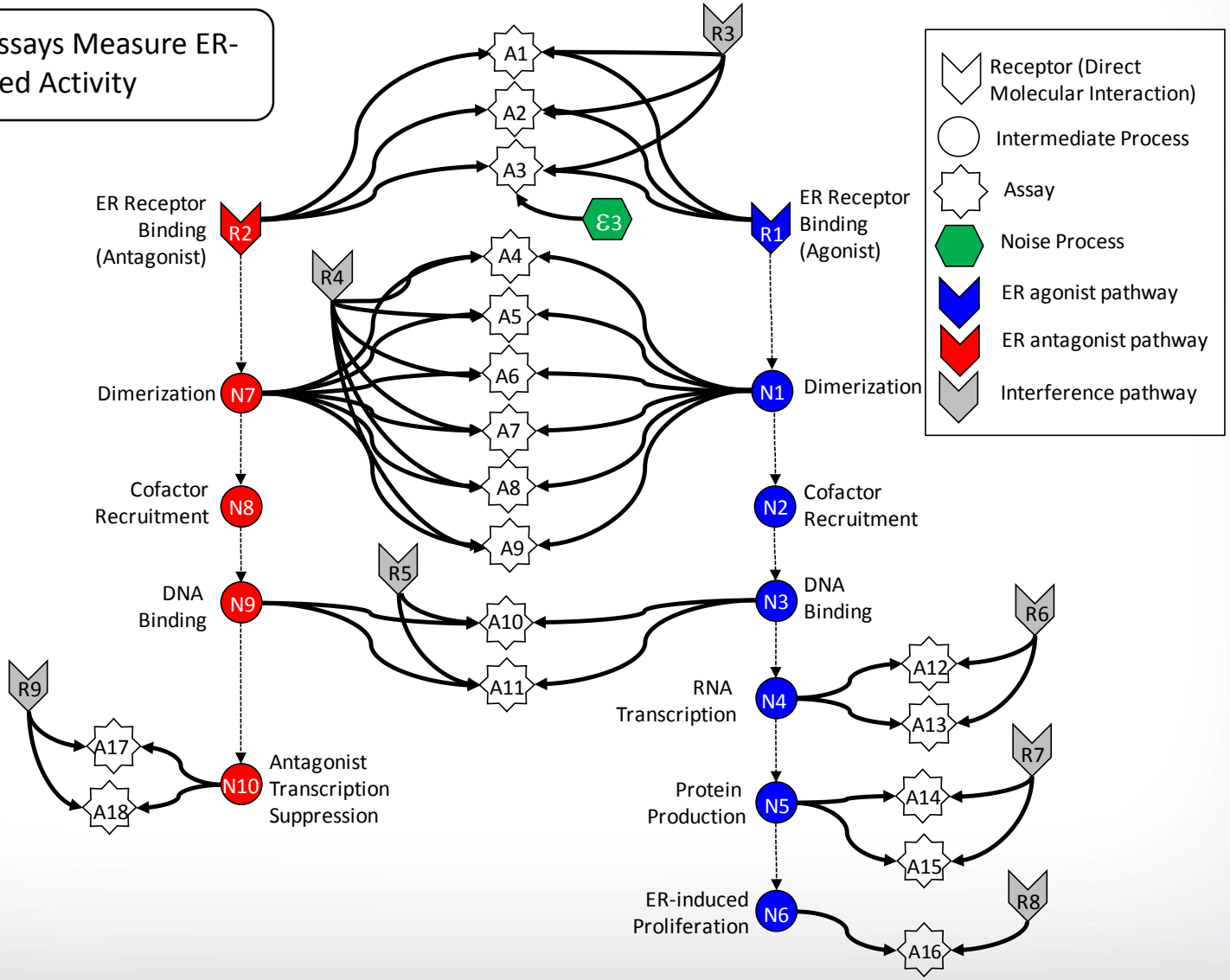




Thomas *et al., Tox Sci.,* 2013

Estrogen-Activity as an Example of Selective Chemical Analysis

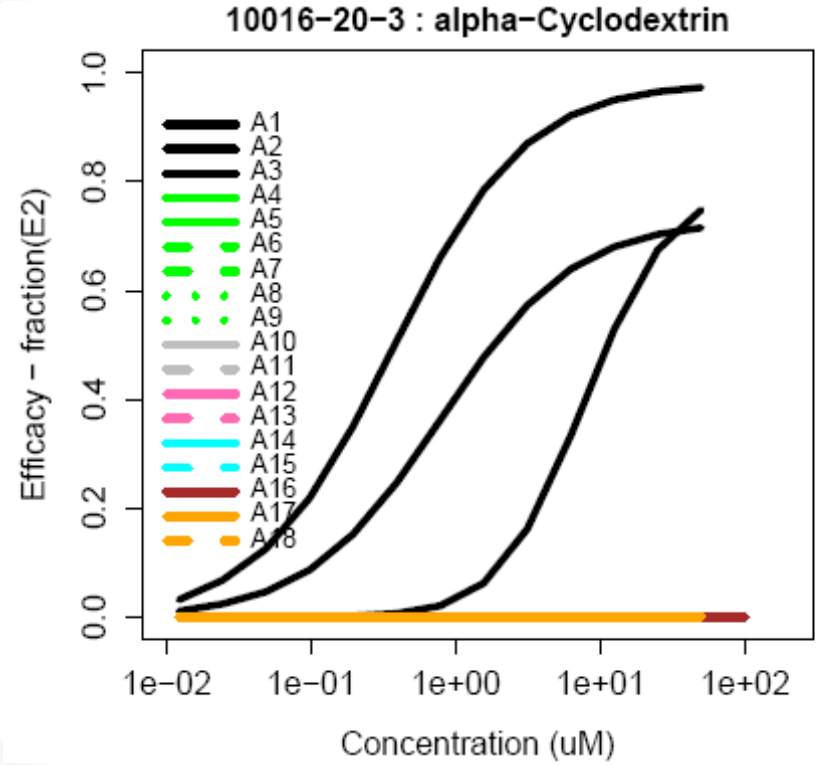
18 *In Vitro* Assays Measure ER-Related Activity



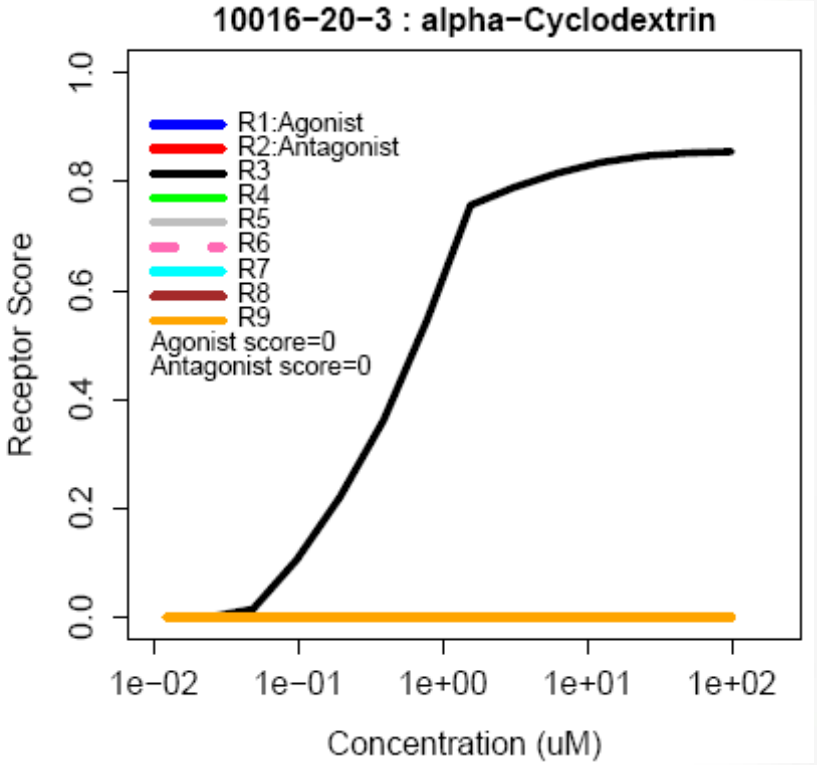
Unpublished Data

Assigning Assay Results to Receptor Agonist or Antagonist Activity

Assays

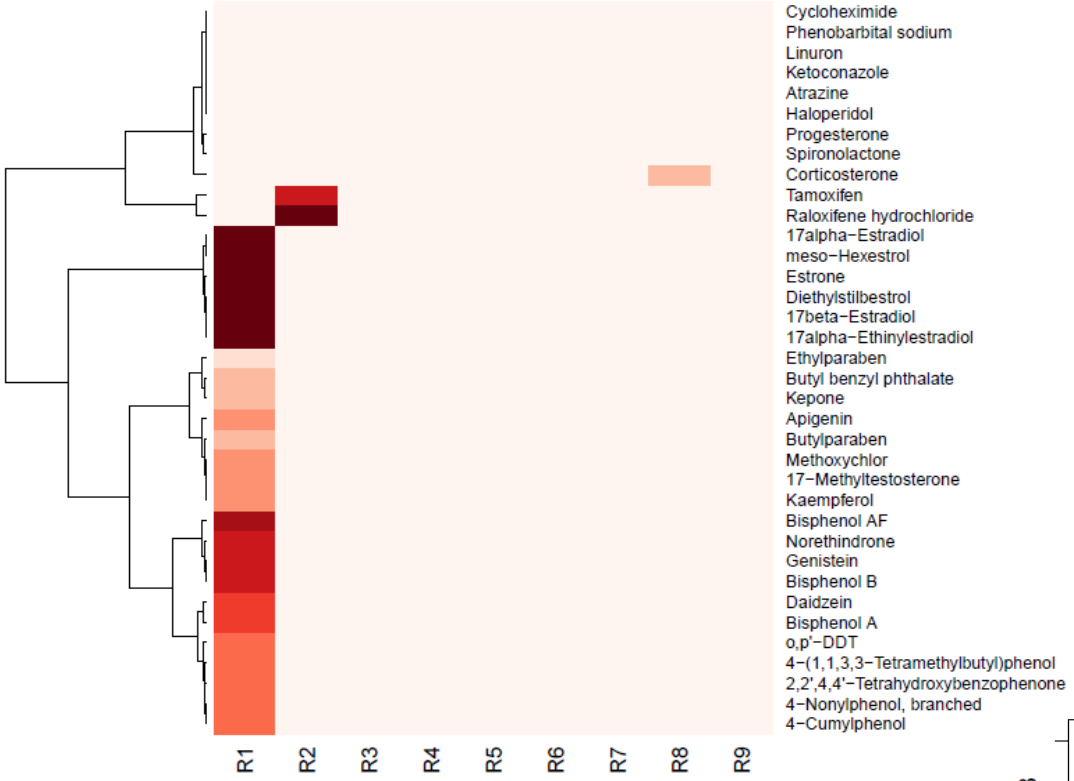


"Receptors"

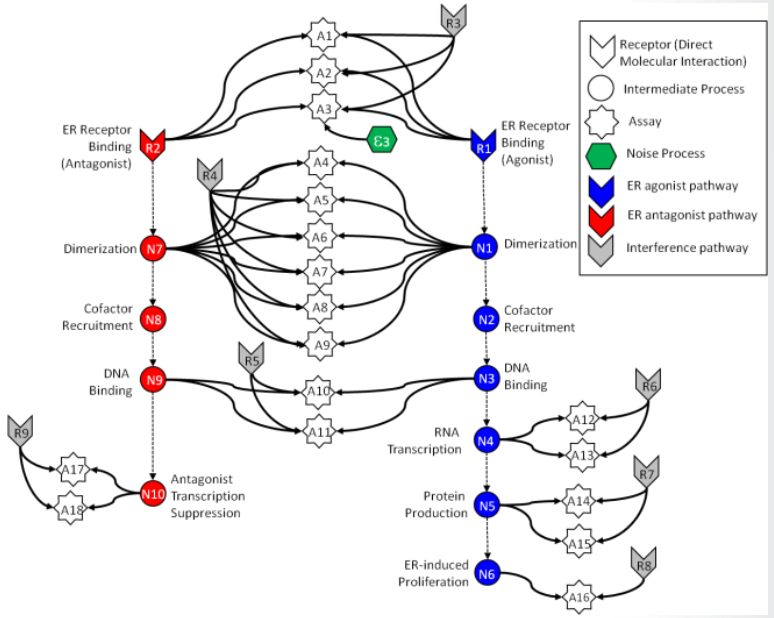


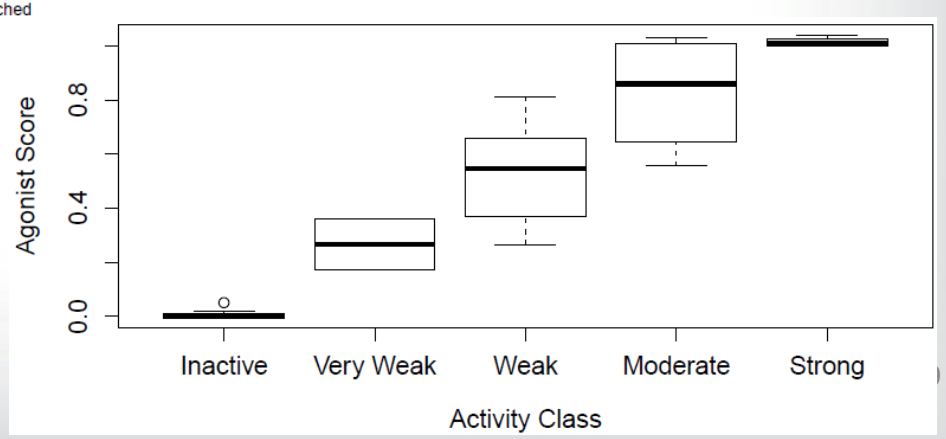
Unpublished Data

Model Benchmarking Against Standard Reference Chemicals



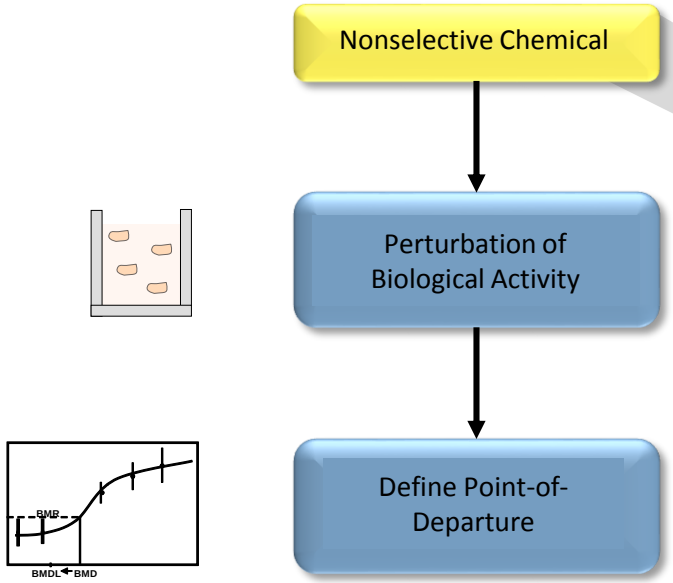
Heat Map of Score for Reference Chemicals

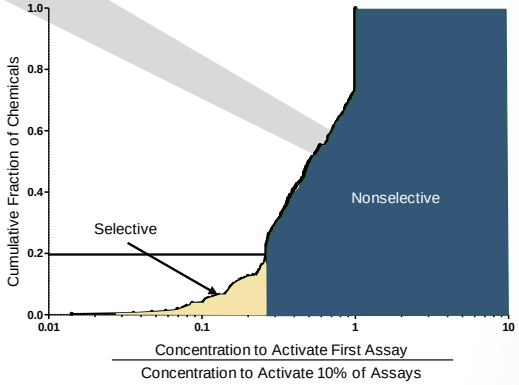




Unpublished Data

Non-Selective Chemicals Evaluated Based on Gross Biological Activity





Thomas *et al., Tox Sci.,* 2013

Converting *In Vitro* Concentrations into Administered Doses

309 EPA ToxCast Phase I Chemicals

Human Liver Metabolism

Human Plasma Protein Binding

Population-Based IVIVE Model

Upper 95th Percentile Css Among 100 Healthy Individuals of Both Sexes from 20 to 50 Yrs Old

ToxCast AC_{50} Value

Plasma Concentration

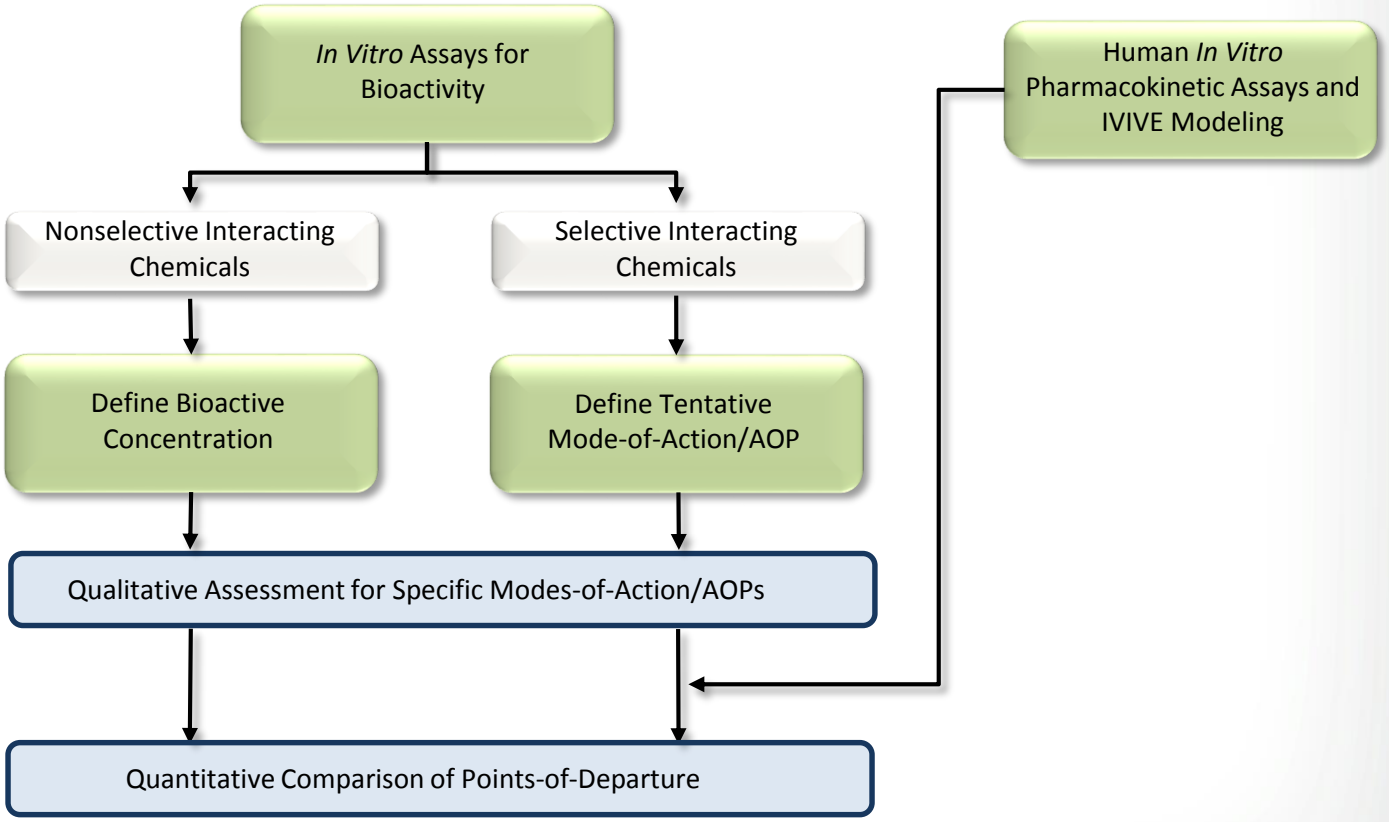
Oral Exposure

Reverse Dosimetry

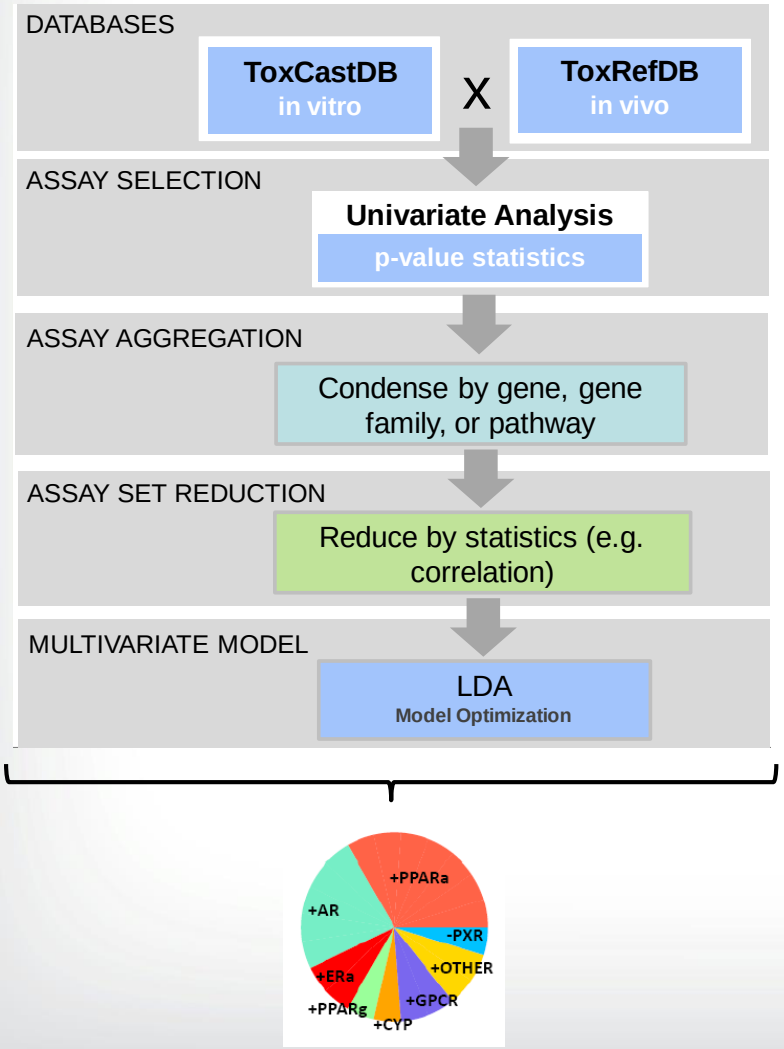
Oral Dose Required to Achieve Steady State Plasma Concentrations Equivalent to *In Vitro* Bioactivity

Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.,* 2012

Integrating *In Vitro* Data for Qualitative and Quantitative Alternatives Evaluation

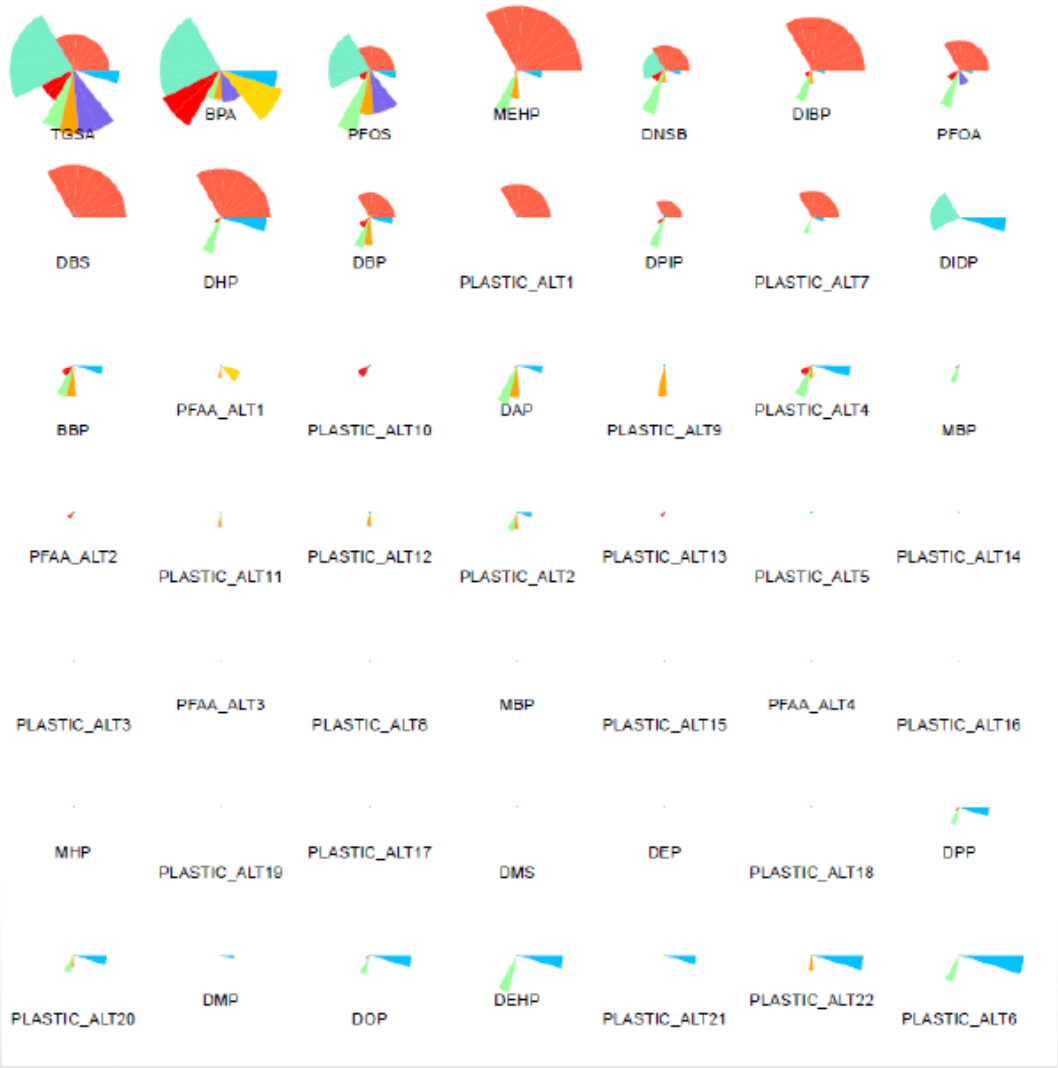


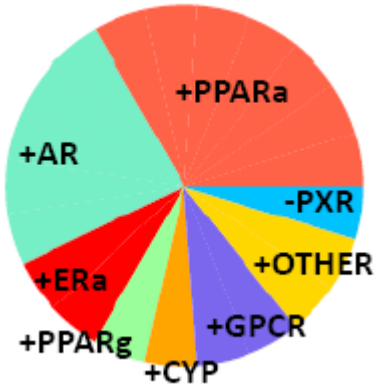
Example of Using *In Vitro* Assay Data for Qualitative Evaluation of Alternatives



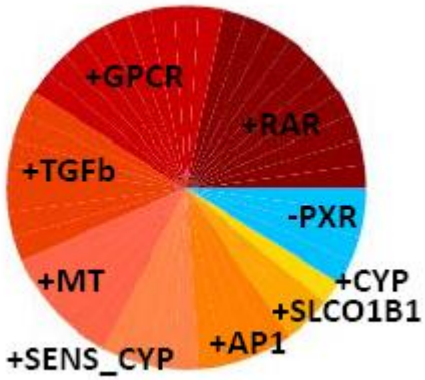
- Statistical classification models for developmental and reproductive toxicity endpoints
  - Sipes *et al.*, *Tox Sci.*, 2011
  - Martin *et al., Biol Reprod.,* 2011
- Assays from models used to evaluate 52 ToxCast chemicals and plastic alternatives
- Each slice of the ToxPi represents multiple assays ordered based on the model score
- Weighting factors and assays were used per the publications, except the human CYPs replaced the rat CYPs in the repro model, and the BSK assays were removed.

Prioritizing Alternatives Using Assays Associated with Reproductive Toxicity





Prioritizing Alternatives Using Assays Associated with Developmental Toxicity



Questions…

1. In what context (e.g., substitution/"new chemical" design) can your analysis be used?
2. What data streams can be potentially incorporated into such an analysis?
3. What is the ultimate output of such analysis? Is it qualitative or quantitative?
4. What is the strategy for an end-user to make a decision? How will the end-user decide what results, data, or endpoints are most "important" or informative?
5. How can the information on data quality and or underlying uncertainties (e.g., noise in the assay) be integrated into the output?